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Long-term clinical outcomes in a cohort of adults with childhood-onset Systemic Lupus Erythematosus

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Short title: Long term clinical outcomes in adults with childhood-onset SLE.

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Abstract

Objective: Childhood-onset SLE (cSLE) is a severe lifelong multisystem autoimmune disease. Long-term outcome data are limited. Here, we report clinical characteristics and health-related quality of life (HRQOL) of adults with cSLE.

Methods: Patients underwent a single study visit comprising a structured history and physical examination. Disease activity (SLEDAI-2K), damage (SLICC-Damage Index (SDI)) and HRQOL (SF-36) were determined. Medical records were retrieved.

Results: In total, 111 cSLE patients were included, median disease duration 20 years, 91% female and 72% white. Disease activity was low (median SLEDAI 4), 71% of patients used prednisone, hydroxychloroquine and/or other disease-modifying anti-rheumatic drugs. The

vast majority of new cSLE-related manifestations developed within 2 years of diagnosis. Damage like myocardial infarctions started occurring after 5 years. Most patients (62%) had damage, predominantly in the musculoskeletal, neuropsychiatric and renal systems. Cerebrovascular accidents, renal transplants, replacement arthroplasties and myocardial infarctions, developed at young age (median age 20, 24, 34 and 39 years respectively). Multivariate logistic regression showed that damage accrual was associated with disease duration (OR=1.15;p<0.001), antiphospholipid-antibody positivity (OR=3.56;p=0.026), and hypertension (OR=3.21;p=0.043). Current HCQ-monotherapy was associated with an SDI-score of 0 (OR=0.16;p=0.009). HRQOL was impaired compared to the Dutch population. Presence of damage reduced HRQOL in one domain. High disease activity (SLEDAI≥8) and changes in physical appearance strongly reduced HRQOL (4/8 and 7/8 domains).

Conclusions: The majority of adults with cSLE in this large cohort developed significant damage at young age and have impaired HRQOL without achieving drug free remission, illustrating the great impact of cSLE on future life.

Systemic lupus erythematosus (SLE) is a lifelong multi-system autoimmune disease, known for its highly heterogeneous clinical presentation and waxing-waning disease course. Childhood onset SLE (cSLE), defined as SLE with onset < 18 years (1), represents 10-20% of all SLE-cases with a mean age at onset of 11-12 years (2, 3). CSLE is a rare disease with an incidence ranging from 0.3 – 0.9 per 100.000 person-years, and prevalence of 1.89 to 25.7 per 100,000 children worldwide (reviewed in (4-6)). Similar to SLE in adults, cSLE is seen more often in non-whites and girls (female-male ratio 4-5:1). Disease manifestations differ among ethnicities, but clinical outcomes like disease activity and damage tend to be similar when corrected for socio-economic status (7-10).

Although survival of cSLE patients has greatly improved, morbidity is still high and questions from children and parents regarding the future course of the disease are difficult to answer (7, 11). Long-term follow-up studies of cSLE patients are limited and often have low patient numbers and/or include patients with a relatively short disease duration, and detailed evidence regarding development of new organ involvement and damage over time is lacking (7, 12-17). Overall, these studies show that the majority of adolescents and young adults with cSLE still have active disease, use immunosuppressive drugs and steadily accrue damage during their disease (7, 11, 12, 18, 19). Only one North American cohort study of both cSLE and adult-onset SLE patients, has included a large number of cSLE patients (n= 90) with long disease duration (mean 16.5 years) and compared outcomes of cSLE to adult-onset SLE (18). In this study, structured telephone interviews were used to collect patient-reported clinical outcomes, of which only significant renal outcomes could be validated by chart review. At the time of study interview, cSLE patients had lower disease activity and were more likely to have ever received and currently be treated with corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs) when compared to adult-onset SLE patients (18). This was also seen in a cohort comparing cSLE, adult-onset SLE and late-onset SLE patients with a disease duration of 12 years (19). In the North American cohort of adult-onset and cSLE patients, cSLE was shown to be an independent risk factor for mortality (11). Due to the nature of this cohort study with primarily patient-reported clinical outcomes, data regarding development of damage could not be given.

In children with cSLE, health-related quality of life (HRQOL) has been shown to be impaired compared to healthy peers, which was at least partially attributed to disease activity and damage (20, 21). There are no data available regarding HRQOL in patients with cSLE after reaching adulthood, and which factors could influence HRQOL in these patients.

The Childhood-onset SLE in the Netherlands (CHILL-NL) study aims to assess the burden of disease of cSLE in the Netherlands. In this article, we describe the clinical characteristics of adults with cSLE, focusing on disease course and damage accrual over time in association with HRQOL.

Patients and methods

Patients. All cSLE patients > 18 years who were treated in any Dutch hospital and met the ACR-criteria for SLE (22, 23) were eligible for inclusion in the CHILL-NL study. Rheumatologists, immunologists, nephrologists, haematologists, and neurologists in all 88 Dutch hospitals were contacted. There are hardly any private practices in the Netherlands. In addition, as SLE is a systemic disease where hospital diagnostics are essential for optimal treatment, rheumatologists in private practices in general do not treat SLE patients. Therefore these practices were not contacted. All medical specialists in secondary or tertiary hospitals were contacted via e-mail and folders. They were asked to identify patients with SLE in their care that were diagnosed prior to their 18th birthday, and ask these patients if they were interested in participation in a study on long-term outcome of their disease. The study was also promoted in the magazine and on the website of the Dutch SLE patient organization (24). Due to the study design, data regarding mortality of cSLE or clinical characteristics of deceased patients could not be retrieved reliably; therefore this study only reports data from surviving patients. The Research Ethics Board of the Erasmus Medical Centre approved the study (MEC-2013-163) and written informed consent was obtained from all patients.

Data collection

The CHILL-NL study team designed the study with the help of a patient panel (n=5). All patients were seen for a single, 1.5-hour study visit in the Erasmus Medical Centre. If patients were not able to travel, the study visit was performed at the hospital of the patients' choice. During the study visit, an extensive medical history was taken using structured data collection forms and (validated) questionnaires. Data regarding demographics, current health, disease activity, damage, disease onset and progression over time, current and previous medication use were collected. Physical examination was performed, blood and urine were collected, and the patients completed questionnaires regarding health-related quality of life (HRQOL), effects of medication use on physical appearance, physical health or mental health (yes/no and open area for explanation), education and employment, fertility and family planning, fatigue, depression, coping and resilience (25-30). For this article, a selection of the data was used as defined in the outcomes. Medical information was requested from any hospital where patients had received care. Clinical data collected during the study visit was supplemented and verified with the retrieved medical history. Only data that could be verified in the medical records are reported.

Demographics. Data regarding demographic characteristics such as age, sex, self-reported ethnicity and area of residence were collected by structured questionnaires. Categories of ethnicity included African/Caribbean, Arabic, Asian, Hispanic, white and mixed. .

Outcomes

In this article, we focus on disease activity, medication use, disease manifestations over time, damage, HRQOL.

Diagnosis, disease manifestations and damage over time. Number of ACR and SLICC criteria and any other cSLE-related manifestations at diagnosis were registered (22, 23, 31). Definitions of disease manifestations are listed in the legend of Figure 1. Disease duration was defined as the years between study visit and date of diagnosis as reported in the medical records. Based on findings in previous studies, disease manifestations of cSLE over time were recorded according to six predefined time-frames (7, 32, 33): i) never, ii) prior to diagnosis, iii) at diagnosis, iv) <2 years since diagnosis, v) 2-5 years since diagnosis and vi) >5 years since diagnosis. Age at first myocardial infarction, renal transplantation, cerebrovascular accident (CVA) and replacement arthroplasty was derived from the medical records. Specific disease manifestations such as antibody positivity were recorded as positive or negative if this was found in the medical records, and unknown if this was not mentioned in the records. Nephrotic syndrome was recorded to be present if clinical manifestations (oedema, proteinuria (3-3.5 g/24 hour) and hypoalbuminemia <25 g/L) were present , or if the medical records stated a patient to have had nephrotic syndrome. Hypertension was recorded to be present when patients had persistent blood pressures over 140/90 mmHg or when the medical records stated patients to have hypertension.

Disease activity and medication use. Disease activity was assessed using the SLEDAI-2k (34). High disease activity was defined as SLEDAI≥8 (35, 36). Additionally, patients were asked to rate their disease activity on a visual analogue scale (VAS), ranging from 0 (no disease

activity) to 100 (very high disease activity). Medication use was classified as current use, previous use and never used. Corticosteroid and hydroxychloroquine (HCQ) were considered separately. Non-HCQ DMARDs were defined as azathioprine, ciclosporin, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, rituximab and tacrolimus. All other medication use, including antiepileptic medication, antihypertensive drugs including angiotensin-converting-enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) and coumarins was also registered. Patients were asked in an open ended question during the study visit if there were any medications that had affected them regarding their physical appearance, physical or mental health, and in what way they were affected.

Damage. Disease damage was assessed with the SLE International Collaborating Clinics (SLICC)/ACR Damage Index (SDI) (37). Presence of damage was defined as SDI score ≥1. If damage had a specific temporal component (i.e. cognitive impairment, renal impairment present for at least six months), it was recorded if the item was found in two consecutive reports from the medical records.

HRQOL. HRQOL was assessed using the Short-Form-36 (SF-36), which includes 36 questions in 8 health domains: Physical Functioning (PF), Social Functioning (SF), Role limitations due to Physical problems (RP), Role limitations due to Emotional problems (RE), Mental Health (MH), Vitality (VT), Bodily Pain (BP) and General Health Perception (GH) (25). HRQOL-scores of patients were compared to the general population. Effect of disease activity (low (SLEDAI ≤4), intermediate (SLEDAI 5-7) and high (SLEDAI≥8)) (35), SLEDAI-items concerning changes in physical appearance (ongoing inflammatory rash and/or alopecia) and damage on HRQOL was assessed.

Statistical analysis

Group comparisons were made using the Mann-Whitney-U (MWU) or the Kruskall-Wallis (KW) test where applicable. One sample t-tests were used for comparisons with normative data from the Dutch population. Logistic regression analysis was performed to assess associations of individual variables and the development of damage. Selection of these variables was based on literature (reviewed in (38)). Presence of damage was defined as outcome, pre-determined variables were covariates in the model. Variables with an individual effect of $p<0.1$ were used to build the multivariable model, using a hierarchical entry method. In the final, most parsimonious model, variables with an association of $p<0.05$ were considered to contribute. To assess goodness of fit, the Hosmer-Lemeshow test was used, and residual statistics (Cook's distance standardized residuals, deviance and leverage) were analysed. All analyses were performed using IBM SPSS Statistics v22 (SPSS Inc, Chicago, IL, USA)

Results

Patients

Patient inclusion: Patients were included in the CHILL-NL study from November 2013 until April 2016. Eighty-eight secondary and tertiary hospitals were contacted. Doctors from 18 hospitals confirmed to have adults with cSLE under their care and sent contact information of 121 patients to the study team. An additional 15 patients contacted the study team via the patient organization. Of these 136 patients, 111 (82%) were seen for a single study visit. (supplementary figure 1). As an example for the proportion of study participants included in

the study to those treated at a certain site: at the Erasmus University center, 23 adults with cSLE are treated, of which 17 (74%) participated in the CHILL-NL study.

Most study participants (69%) were treated in a tertiary centre (supplementary figure 1). Forty percent of patients lived within the vicinity of the Erasmus Medical Centre. Residences of the remaining patients were equally distributed over the rest of the country.

Demographics: Median age at study visit was 33 years, with median disease duration of 20 years (table 1). Year of diagnosis ranged from 1959 to 2013. Patients were divided into 3 diagnostic eras according to year of diagnosis. The number of patients in each group was equally distributed with 67% of patients being diagnosed before 1990. The most common ACR criteria at diagnosis were ANA-positivity, immunological features, and arthritis (supplementary figure 2). Almost all participants were female (91%). The majority of patients were white (72%), 10% were African/Caribbean, 7% Asian, 3% Hispanic, 1% Arabic, and 7% had a mixed heritage. Due to the majority of patients being white, ethnicity was dichotomized in white and non-white. These groups did not differ regarding age at onset and disease duration.

Medication use: The vast majority of patients (68%) still used corticosteroids and/or non-HCQ DMARDs at study visit (table 1). Regarding corticosteroid-use, 56 of 111 patients (51%) used corticosteroids with or without non-HCQ DMARDs. Of all 111 patients, 68% (76/111) currently used HCQ, of whom 29% (22/76) used HCQ monotherapy. Sixty-five percent of patients used other, non-anti-inflammatory medications, including anti-hypertensive medication (including ACE-I and ARB) (51%), statins (14%), coumarins (14%), acetylsalicylic

acid (12%), antidepressants (8%) anti-epileptic medication (5%) and/or erythropoietin (5%). When asked about the effects of medication use on physical appearance, physical health or mental health, the majority of patients reported to have been impacted negatively. The largest impact was reported on physical appearance (89%), which was perceived negatively by 93% of the patients. They also reported a negative impact on physical health (36%) and mental health (28%). Effects on physical appearance (e.g. weight gain) as well as mental health (e.g. mood swings) were mostly attributed to prednisone use. Effects on physical health (e.g. nausea) were mostly attributed to non-HCQ DMARDs.

Disease activity: Disease activity was relatively low at study visit (median SLEDAI-score 4, median VAS 13). Low complement (32%), skin rashes (14%) and proteinuria (13%) were the most common SLEDAI items recorded. No difference was found between the SLEDAI-scores of patients using corticosteroids and/or non-HCQ DMARDs, patients using HCQ monotherapy or patients using no corticosteroids/non-HCQ DMARDs/HCQ (KW p=0.177).

Infections: Almost half of the patients (50/111) had been admitted to the hospital due to infections requiring intravenous antibiotic therapy during their disease course, and 48% was admitted more than once (table 1).

Disease manifestations and damage over time

Organ systems which were most frequently involved, were the skin (e.g. malar or discoid rash, cutaneous vasculitis), musculoskeletal system (mainly arthritis), haematological system (e.g. haemolytic anaemia, leukopenia) and renal system (e.g. lupus nephritis). The vast majority of new disease manifestations in these organ systems (i.e. skin, musculoskeletal,

haematological and renal) developed within 2 years (figure 1). Cardiovascular, pulmonary and central nervous system (CNS) manifestations occurred short- as well as long-term. However, within two years of diagnosis, pericarditis, pleuritis and epilepsy were the most common manifestations within these organ systems, whereas 5 years after disease diagnosis damage was most prevalent (myocardial infarction and CVAs). Manifestations of peripheral nervous system and gastro-intestinal system were uncommon and mainly occurred 5 years after diagnosis.

Disease damage

In total, 62% percent of the patients had developed damage. Renal, neuropsychiatric and musculoskeletal damage were most prevalent (figure 2A). The percentage of patients with damage increased over time (figure 2B). Regarding the development of damage of specific organ systems per period of disease duration, musculoskeletal (e.g. avascular necrosis, deforming/erosive arthritis), neuropsychiatric (mostly cognitive impairment, often combined with seizures requiring treatment >6 months) and renal damage (e.g. end-stage renal disease) were most prevalent (figure 2C, supplementary table 1).

Notably, after 10-20 years, when cSLE patients are in their early twenties/thirties, significant damage had occurred in more than half of the patients (figure 2C, supplementary table 1). At a median age of 20 years, seven cSLE patients (5%) had suffered a CVA. Sixteen of 67 (24%) patients who had renal involvement during their disease, subsequently developed damage (supplementary table 2). Of these 16 patients, 38% received a renal transplant (median age 24 years). One patient was on renal replacement therapy. Six patients underwent replacement arthroplasty in one joint, and four patients received more than one

joint replacement. Median age at first joint replacement was 34 years. Five patients had a myocardial infarction at a median age of 39 years. Three of them also underwent coronary bypass surgery (supplementary table 2).

Factors related to the development of damage

Logistic regression analysis was performed to assess associations between individual variables and development of damage (table 2). Univariate analysis showed longer disease duration, and presence of antiphospholipid antibodies (aPL) positivity, infections requiring hospitalization (ever), presence of hypertension (ever) and presence of nephrotic syndrome (ever) were associated with the presence of damage. Neither gender nor ethnicity had a significant association with presence of damage. Current HCQ monotherapy was associated with the absence of damage. In the multivariate analysis, disease duration (OR 1.147, 95% CI 1.077-1.227, p<0.001), hypertension (OR 3.214, 95% CI 1.040-9.932, p=0.033) and aPL-positivity (OR 3.559, 95% CI 1.161-10.908, p=0.026) were significantly associated with presence of damage, and current HCQ monotherapy (OR 0.162, 95% CI 0.042-0.633, p=0.009) was again associated with the absence of damage. No differences in number or type of organ system involvement or anti-inflammatory medication use were found between patients currently using HCQ monotherapy and other patients.

Health-related quality of life

HRQOL as measured with the SF-36 at study visit was lower in adults with cSLE on 6/8 domains when compared to the Dutch population (figure 3A). Low disease activity, defined as SLEDAI ≤4, positively affected HRQOL (figure 3B). A more detailed evaluation of SLEDAI-items concerning changes in physical appearance (SLEDAI-items ongoing inflammatory rash

and/or alopecia (n=25)) revealed a clearly negative impact on HRQOL in 7/8 domains (figure 3C). Notably, HRQOL in these patients was similar or even lower than in those with high disease activity (SLEDAI≥8), even though only 24% of patients with changes in physical appearance had high disease activity. An active renal component in the SLEDAI (n=14) did not affect HRQOL. No differences were seen in HRQOL between white and non-white patients (data not shown). Remarkably, HRQOL was not different in patients with or without damage in 7/8 domains, with significantly lower scores only in the Physical Functioning domain (figure 3D). Physical functioning domain scores of patients with very long disease duration (>30 years) were worse compared to patients with short disease duration (<10 years). On the other hand, Mental Health domain scores improved over time, with higher scores in patients with a long disease duration (data not shown).

Discussion

This is the first study reporting data regarding disease manifestations over time, damage and HRQOL in a large cohort of predominantly white adult patients with cSLE with very long disease duration.

Most patients had low disease activity but still used DMARDs and/or corticosteroids 20 years after diagnosis. More than half of the patients also used medications to treat non-inflammatory disease or damage-related symptoms. Clearly drug-free remission remains difficult to achieve, and current DMARDs are not effective enough to be used without corticosteroids in many patients. Indeed, half of patients were still using corticosteroids with or without DMARDs, as was reported in other cohorts (cSLE and SLE) with mean disease duration of 12 to 16 years (18, 19). This is worrying as corticosteroids are associated with

the development of damage (39). Patients are certainly eager to limit corticosteroid use, as almost all patients in the CHILL-NL cohort reported to have negative experiences with prednisone regarding their physical appearance and/or mental wellbeing. Although these findings may be influenced by recall bias, they clearly illustrate the perceived impact of corticosteroid use on a patient's wellbeing, thereby underlining the need for the development of new treatment strategies that will be able to further limit or even eliminate corticosteroid-use.

Most organ systems became involved within the first two years of diagnosis. Thereafter, hardly any new cSLE-related manifestations occurred in organ systems not previously affected. This finding was also reported in two cSLE cohorts, but these cohorts only had a mean disease duration of four years (32, 40). After 5 years of disease, we showed that the nature of disease manifestations shifts to damage such as myocardial infarction, instead of primary disease related manifestations like pericarditis or epilepsy. This shift to damage has also been observed in adult-onset SLE patients (41-44) and urges for preventative screening measures of such (cardiovascular) damage and healthy life-style advice (healthy diet, regular exercise, abstinence from smoking). A study looking at (laboratory) markers of cardiovascular risk in adolescents with cSLE found that disease duration and signs of renal injury (e.g. proteinuria, history of hypertension) were associated with markers of cardiovascular risk (45). As we and others show that cardiovascular damage starts occurring in patients' twenties/early thirties, prevention strategies must be considered during transition to adult care, especially in patients with renal involvement (12, 18). As infections are common in cSLE patients and related to mortality (46, 47), infection prevention by vaccination should be actively advocated (48, 49).

The majority of the patients had developed damage in their mid-twenties and this percentage increased with longer disease duration. The musculoskeletal system, kidneys and CNS were most frequently affected, as in other cSLE studies albeit describing patients with limited disease duration (5-10 years) (13, 15, 16, 19, 50). The only available studies reporting damage in patients with mean disease duration of ≥20 years were performed in adult-onset SLE (50, 51). Reported frequency and characteristics of damage in these cohorts were similar to the results in the CHILL-NL cohort. However, the mean age of diagnosis in the adult-onset SLE cohorts was 31 years (50, 51) versus 14 years in our cohort, reflecting that most patients with cSLE had started to develop significant damage in their early twenties. This is underlined by results from two North-American cSLE-cohorts (mean disease duration of 5 years and 16.5 years) that reported myocardial infarction in cSLE patients in their early twenties/thirties (12, 18).

Disease duration was the main variable associated with the development of damage in the CHILL-NL cohort, next to aPL positivity and hypertension. This is consistently reported in many other (c)SLE studies (13, 15, 50-53). Presence of damage did not differ between white and non-white patients. Other studies show conflicting results regarding ethnicity and development of damage (7, 9, 12). Similar socio-economic status of white and non-white patients could possibly explain the lack of association of ethnicity with damage (7-11). Due to the low number of men, this study is underpowered to report associations of gender with damage. Current HCQ monotherapy was associated with the absence of damage, although no information regarding the duration of HCQ monotherapy was registered. Therefore we cannot be sure that the group currently on HCQ monotherapy reflects a group of patients with mild disease. This is underlined by the lack of association of organ involvement and

anti-inflammatory medication use ever between the patients currently on HCQ monotherapy and the other patients. Longitudinal cohort studies are necessary to clarify this issue further. Notably, the association of damage with disease duration also reflects past and current treatment modalities. Patients with long disease duration may have developed more damage over time due to treatment strategies that are now uncommon and more recently diagnosed patients may have had the opportunity to profit from improved treatment strategies that lead to less damage. The cross-sectional design of this study does not allow dissecting the positive effects of improved treatment modalities from the negative effects of disease duration on the development of damage.

This is the first study assessing HRQOL in cSLE patients after reaching adulthood. HRQOL was impaired in most domains when compared to the general Dutch population. Other studies in children with cSLE and adult-onset SLE patients also showed that patients had an impaired HRQOL (21, 54-56) and HRQOL was similar or even lower when compared to patients with other chronic illnesses (54-57). A possible explanation for the similar mental and emotional health scores in the CHILL-NL cohort might be the development of resilience in the patients at a young age to the emotional impact of their disease, as perceived HRQOL can be affected by different styles of coping (58). High disease activity (SLEDAI≥8) had a significant negative effect, which is supported by other studies (20, 21, 57, 59). Interestingly, an even larger negative effect on HRQOL was seen with regard to factors affecting physical appearance. Indeed, two other studies showed that changes in physical appearance (e.g. obesity, skin involvement) are associated with reduced HRQOL (60, 61). Surprisingly, the presence of damage hardly affected HRQOL, with only physical functioning being significantly reduced. Other studies did show a negative association of damage with HRQOL

(21, 52). This discrepancy might be explained by the heterogeneous nature of the developed damage that may differ between cohorts, but also to development of adequate coping-styles in cSLE patients who have learned at an earlier age to adjust their life-style to the extent of their damage.

The CHILL-NL study has several strengths. It is a large cohort, and all patients were seen in person, providing the possibility to verify disease activity and damage by laboratory analysis and physical examination. Medical records were retrieved for all patients, with which all reported outcomes were verified. The lack of studies in adults with cSLE show that it is challenging to identify patients after transferring to adult care. Even the North-American cohort reporting on outcomes of adult cSLE patients has not been designed to specifically recruit adults with cSLE (62). This is therefore the largest cohort of cSLE patients with very long disease duration that reports on verified disease characteristics as well as HRQOL.

The limitations of the CHILL-NL study must also be addressed. First, the number of patients who were not interested in participating in the study and as such were not referred to the study team, was unknown. It must be noted that the patients included in this study are not a random selection of the total cSLE population in the Netherlands. Patients from both ends of the severity spectrum, i.e. patients with severe disease, as well as patients with mild disease who do not visit a physician regularly, will be missed in this cross-sectional study design. Patients with high disease activity or severe damage may not have participated in the study, as it could be seen as too taxing. To overcome this limitation, we offered to travel to the patient if they indicated that travel distance was seen as a barrier. Of the patients who were referred to the study team, the great majority participated in the study. Second,

due to the cross-sectional nature of the study, deceased patients were missed. As disease severity is a risk factor for mortality (11, 50), it is possible that we have a bias towards less severe disease in our cohort. This could explain the relatively low renal involvement in the CHILL-NL cohort compared to other cSLE studies. Third, data for this study were collected retrospectively, and information could have been missed. We chose only to report disease characteristics that could be verified with medical records. No data could be collected from deceased patients. Consequently, the results from the CHILL-NL study will more likely be an underrepresentation than an overrepresentation of the severity of the disease. These limitations illustrate the need for longitudinal cohorts that follow cSLE patients even after transfer to adult care (12).

In conclusion, the CHILL-NL study shows that cSLE has a major impact on adult life. This is the first study to give insight into the development of disease manifestations and damage over time in adults with cSLE and their HRQOL. cSLE-related manifestations developed mostly within 2 years of diagnosis, with a shift to development of damage 5 years after diagnosis. Major medical complications (i.e. renal transplants, CVA, myocardial infarction) occurred at young age. These results urge for optimal control of disease activity and (cardiovascular) preventative screening measures, starting before the age of thirty, to facilitate a better disease prognosis. HRQOL of adults with cSLE is impaired and affected by other factors than disease activity or damage alone. By identifying and addressing these factors, like physical appearance and potentially coping styles, HRQOL may be improved.

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Tables

Table 1. Patient characteristics at study visit

Characteristics	**Number (%) of total (n=111)***	
Female	101 (91%)	
Ethnicity		
White	80 (72%)	
Non-White	31 (28%)	
Age at diagnosis in years, *median (range)*	14 (4 – 17)	
Age at study visit in years, *median (range)*	33 (18 – 65)	
Disease duration in years, *median (range)*	20 (1 – 55)	
Era of diagnosis		
Prior to 1990	37 (33%)	
Between 1990-2000	38 (34%)	
After 2000	36 (32%)	
		Patient VAS *(median, range)*
SLEDAI-2K *(median, range)*	**4 (0 – 16)**	**13 (0-95)**
patients with SLEDAI ≤ 4	72 (65%)	10 (0-95)
patients with SLEDAI 5 – 7	23 (21%)	23 (0-85)
patients with SLEDAI ≥ 8	16 (14%)	33 (0-75)
Current corticosteroid/non-HCQ DMARD[‡] use	**75 (68%)**	
Corticosteroids + non-HCQ DMARD	40/75 (53%)	
Corticosteroids only	16/75 (21%)	
Non-HCQ DMARD only	15/75 (20%)	
2 non-HCQ DMARDs +/- corticosteroids	4/75 (5%)	
Current HCQ use	**76 (68%)**	
HCQ + non-HCQ DMARD/corticosteroid	54/76 (71%)	
HCQ monotherapy	22/76 (29%)	
No HCQ/corticosteroids/ non-HCQ **DMARD[Δ]**	**14 (13%)**	
SDI *(median, range)*	**1 (0 – 8)**	
SDI ≥ 1	69 (62%)	
Infections requiring I.V. antibiotics (ever)	**50 (45%)**	
Once	26/50 (52%)	
More than once	24/50 (48%)	

**If number of patients is not given, percentages are of the total cohort (n=111)*

[‡]*More information regarding specific DMARD-use can be found in supplementary table 3.*

[Δ]*More information regarding these 14 patients can be found in supplementary table 4.*

Abbreviations: HCQ: Hydroxychloroquine; DMARD (Disease Modifying Anti-Rheumatic Drugs): azathioprine, ciclosporin, cyclophosphamide, methotrexate, mycophenolate mofetil, tacrolimus, rituximab; I.V.: Intravenous; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (37); SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index – 2000 (34)

Table 2: Binary logistic regression analysis of variables associated with damage as outcome measure

Predictor (n)	**Univariate**			**Multivariate**		
	β	**OR (95%CI)**	**p**	**β**	**OR (95%CI)**	**p**
Disease duration (111)	0.107	1.113 (1.057-1.171)	<0.001	0.139	1.147 (1.077-1.227)	<0.001
Number of ACR criteria at diagnosis (111)	0.036	1.037 (0.786-1.367)	0.798			
Age at diagnosis (111)	-0.70	0,933 (0.811-1.072)	0.322			
Use of DMARD/corticosteroids with or without HCQ (75) compared to						
HCQ monotherapy (22)	-1.259	0.283 (0.103-0.776)	0.014	-1.818	0.162 (0.042-0.633)	0.009
No HCQ/corticosteroids/ non-HCQ DMARD (14)	-0.185	0.831 (0.251-2.747)	0.761	-0.942	0.390 (0.085-1.787)	0.225
White (80) compared to non-white (31)	0.754	2.215 (0.847-5.329)	0.108*			
Female (101) compared to male (10)	-0.964	0.381 (0.077-1.888)	0.237*			
aPL positivity – Negative (44) compared to						
Positive (48)	0.990	2.692 (1.130-6.417)	0.025	1.269	3.559 (1.161-10.908)	0.026
Unknown (19)	0.539	1.714 (0.569-5.169)	0.338	0.264	1.302 (0.333-5.092)	0.704
Renal involvement – Never (44) compared to						
Within 2 years of diagnosis (50)	0.663	1.94 (0.839-4.490)	0.121*			
After 2 years of diagnosis (17)	0.784	2.191 (0.660-7.268)	0.200*			
CNS involvement – Never (78) compared to						
Within 2 years of diagnosis (9)	1.023	7.515 (1.595-35.423)	0.214*			
After 2 years of diagnosis (24)	0.266	2.088 (0.826-5.276)	0.591*			
Nephrotic syndrome (24) compared to no nephrotic syndrome (87) ever	1.738	5.687 (1.578-20.488)	0.008	0.932		0.242†
Hospitalization (50) compared to no hospitalization due to infection (61) ever	0.505	1.656 (1.098-2.500)	0.016	0.393		0.456†
Hypertension (71) compared to no hypertension (40) ever	1.522	4.583 (1.792-11.715)	0.001	1.167	3.214 (1.040-9.932)	0.043

**A cut-off of p<0.100 was set to select the variables for the multivariate logistic regression. As such, these covariates were not incorporated in the multivariate model.*

†These covariates were not used for the final multivariate model, as they did not improve the fit of the model.

Abbreviations: ACR: American College of Rheumatology; β: regression coefficient; DMARD: Disease-Modifying Anti-Rheumatic Drug; CNS: central nervous system; HCQ: hydroxychloroquine; OR: odds ratio; SDI: Systemic Lupus Erythematosus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (37)

Figures

Figure 1. First occurrence of disease manifestations over time since diagnosis per organ system.

Definitions of disease manifestations: *Skin: malar rash, discoid rash, ulcers, photosensitivity, cutaneous vasculitis, other ongoing inflammatory SLE-related rashes; Musculoskeletal: arthritis, myositis; Haematological: Haemolytic anaemia, thrombocytopenia, leucopenia, lymphopenia, neutropenia, thrombotic thrombocytopenic purpura; Renal: persistent proteinuria, lupus nephritis; Cardiovascular: pericarditis, myocarditis, endocarditis, myocardial infarction, angina pectoris, cerebrovascular accident, transient ischemic attack, arterial thrombosis, venous thrombosis, embolus; Central nervous system: Aseptic meningitis, cerebrovascular disease, demyelinating disease, lupus headache, myelopathy, chorea, convulsions, acute confusional state, anxiety disorder, mood disorder, psychosis; Pulmonary: pleuritic, pneumonia, fibrosis, shrinking lung, pulmonary arterial hypertension, interstitial lung disease; Peripheral nervous system: autonomous nervous system disorder, mononeuropathy, myasthenia gravis, Guillain-Barré Syndrome; cranial nerve neuropathy, plexopathy, polyneuropathy; Gastro-intestinal: peritonitis, pancreatitis, autoimmune hepatitis, liver cirrhosis.*

Figure 2. Disease damage

Damage is defined as SDI≥1, the SDI item definitions were used (37). A: Percentage of patients with damage with subdivision per organ system. B: Number of patients with and without damage, per period of disease duration. C: Percentage of specific cumulative organ

damage relative to the sum of damage scores in all organ systems, displayed per period of disease duration.

Abbreviations: SDI: Systemic Lupus Erythematosus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (37); IDDM: Insulin Dependent Diabetes Mellitus

Figure 3. HRQOL expressed as mean SF36-scores per domain (25)

These spydergrams show mean scores within each domain of the SF-36, ranging from 0 (worst) to 100 (best) (63):

A: SF-36 scores of cSLE patients and the general Dutch population. B: SF-36 scores of patients with low (≤4), intermediate (5-7) and high SLEDAI-scores (≥8). C: SF-36 scores of patients with SLEDAI-scores pertaining to physical appearance (ongoing inflammatory rash and/or alopecia) versus patients without these symptoms and patients with SLEDAI≥8. D: SF-36 Scores of patients with damage (SDI≥1) versus patients without damage (SDI 0).

*p<0.05

Abbreviations: HRQOL: Health Related Quality Of Life; SF36: Short Form-36; cSLE: childhood-onset Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; GH: General Health Perception; PF: Physical Functioning; RP: Role limitations due to Physical problems; BP: Bodily Pain; VT: Vitality; MH: Mental Health; RE: Role limitations due to Emotional problems; SF: Social Functioning